REMARKS

The above claims have been amended to further distinguish over the prior art, and in particular to obviate the obviousness rejection over Nakamichi. This is all further explained below. More specifically, claims 1, 30, 58, 86, 106, and 126 have been amended to state that the compositions defined therein are not dispersions. Support is found in the specification, for example at page 11, lines 19-24.

Attached to this response are pages captioned "Version Marked Up To Show Changes Made", which identify the exact nature of the amendments.

Claims 1-155 stand rejected under 35 USC 103(a) over Piergiorgio, US 4,880,623. The examiner stated, in pertinent part:

> Piergiorgio teaches a composition comprising nifedipine (an anti-hypertensive), polyethylene glycol, hydroxypropylmethyl cellulose and other excipients (abstract and example 2). Piergiorgio teaches that the bioavailability of the drug in the above composition is highly increased. However, Piergiorgio does not teach the drug concentration in the use environment after introduction of the composition in the use environment is 1.25 fold the equilibrium concentration of said drug in said environment. But one of ordinary skill in the art would know routine methods of determining that parameter. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Piergiorgio. One having ordinary skill in the art would have been motivated to prepare the composition of Piergiorgio where the drug displays increased bioavailability in the environment of use. Although, applicants say on page 6, lines 1 and 2 that Piergiorgio does not compare different drug forms, applicants failed to demonstrate that the instant composition displays a higher bioavailability than the composition of Piergiorgio. Examples 1-20 of the application are directed to amorphous drug forms and there is no comparison between the amorphous form and crystalline forms.

The rejection is traversed. One would not find Applicants' invention obvious because Piergiorgio is doing essentially the opposite of Applicants and actually teaches away from Applicants' invention.

Piergiorgio frames his invention against the background of a problem he is trying to solve:

> Due to the low solubility and the high sensitivity to light, Nifedipine presents notable drawbacks in the preparation of stable and bioavailable forms.....Instead, the solid oral forms, tablets, sugar-coated pills, hard gelatine capsules, are absorbed very slowly and consequently are used as retard compositions. However, these are characterized by a bioavailability distinctly inferior to that of the rapid formulations: generally between 40 and 80%. [Column 1, lines 18-29]

Thus, in the above quotation, and by way of background, Piergiorgio explains that slow release ("retard") dosage forms of nifedipine have reduced bioavailability relative to

that of immediate release formulations. Piergiorgio allegedly solves the lowered bioavailability problem with a very specific recipe:

> ...a solution of nifedipine and polyethylene glycol of high molecular weight is made in a common solvent (or mixture of solvents) and the solution is dispersed on a micronized excipient which is soluble in the gastrointestinal juices. [Column 2, lines 14-18].....
>
> Testing the bioavailability, it was surprisingly found that these tablets have the characteristics of a retard product and have a bioavailability equivalent to 100% of the oral forms on the market, wherein the active substance is in liquid suspension in soft gelatine capsules. [column 2, lines 42-47]

At column 3, lines 10-20, Piergiorgio discloses that certain polymers can prolong the "retardant" effect if included in Piergiorgio's compositions. This appears to be the only disclosure in Piergiorgio which bears any relevance to Applicants.

From the above quotations, it is clear that Applicants' are completely distinct with respect to Piergiorgio, and that Piergiorgio's specific combination teaches away from Applicants' generalized compositions. By their invention, Applicants improve a drug's solubility by means of a concentration enhancing polymer combined with a solubility-improved form of the drug. Applicants' teachings are general in the sense that the concentration/bioavailability of drugs in general, and in formulations in general, can be improved by adding a concentration-enhancing polymer to a solubility-improved form of the drug. A given active ingredient in Applicants' composition, by virtue of being combined in a composition with a concentration enhancing polymer, will have a higher concentration, relative to the same composition in the absence of the concentration-enhancing polymer.

Piergiorgio, by contrast, is based on the discovery of a very specific slow release ("retard") composition comprising polyethylene glycol plus nifedipine plus a micronized excipient which restores the concentration of nifedipine back up to that of immediate release formulations. The composition that achieves the restoration need not contain any of the polymers Piergiorgio also discloses that incidentally overlap with the polymers Applicants disclose for use in enhancing concentrations. Those overlapping polymers are disclosed only for prolonging his "retard" (sustained release) effect.

Thus Piergiorgio does not teach increasing the concentration and bioavailability of drugs in compositions generally. He simply teaches a very specific slow release formulation of one drug, nifedipine, which exhibits bioavailability equivalent to that of immediate release nifedipine compositions. Certain polymeric substances, which incidentally overlap with some of Applicants' concentration enhancing polymers, can be

added to "obtain a prolongation of the retard effect" (column 3, lines 10-20 and claim 3). Clearly, whatever Piergiorgio is doing with his polymers, they are not being used to enhance concentration. Rather, they appear to be used as a matrix which adds additional sustained release characteristics to a formulation which is already sustained release. It is doubtful that one skilled in the art would want to use these polymers since, (1) they are not disclosed as being a factor in restoring bioavailability or in increasing drug concentration in Piergiorgio's specific PEG/drug/micronized excipient composition and (2) one skilled in the art would, because the polymers are used to implement additional sustained release, fear degrading bioavailability (note the cautionary note at column 1, lines 18-25). One skilled in the art who wanted to improve the concentration of sparingly soluble drugs generally would simply not find it obvious to do so in the manner Applicants have claimed from a reference which discloses restoring bioavailability of a single drug by means of a specific, different composition having a different purpose.

Claims 1-155 stand rejected for obviousness under 35 USC 103(a) over Nakamichi, US 5,456,923. The Examiner stated, in pertinent part, as follows:

> Nakamichi teaches compositions that comprise solid dispersions of drugs (abstract). The composition further comprises natural or synthetic polymer. The polymer is pH-dependent, pH independent or water-soluble. The polymers include hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate, hydroxypropylcellulose and hydroxypropylmethyl cellulose (column 2, lines 33-59). The drugs which can be used in the invention are antipyretic, analgesic and anti-inflammatory agents, anti-ulcer agents, coronary vasodilators, peripheral vasodilators, antibiotics, anti-spasmodic agents, anti-tussive and anti-asthmatic agents, bronchodilators, diuretics and muscle relaxants (column 3, line 50 to column 5 line 56). The preferred drugs in the invention of Nakamichi are non-heat labile drugs (column 3, line 51). Although, Nakamichi teaches increased bioavailability these drugs, the reference is silent on the concentration of the drug in the use environment following administration compared to the equilibrium concentration of the drug in said use environment. However, one of ordinary skill in the art would know routine methods of determining that parameter. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Nakamichi. One having ordinary skill in the art would have been motivated to prepare the composition of Nakamichi where the drug displays increased bioavailability in the environment of use. Although, applicants say on page 5, lines 4-11 say that Nakamichi teaches amorphous drug forms, applicants failed to demonstrate that the instant composition displays a higher bioavailability than the composition of Nakamichi. Furthermore, examples 1-20 of the application are directed to amorphous drug forms and there is no comparison between the amorphous form and crystalline forms. [Pages 3-4 of the Office Action]

For the sake of completeness, it is noted that not all of Applicants examples relate to amorphous drug forms, as asserted by the Examiner. Examples 1-9 relate to amorphous drugs. Examples 10-14 and 18-19 relate to highly soluble salt forms. Examples 15 and 16 relate to high energy crystal drug forms. Example 17 is related to a drug mixed with a solubilizing agent. Example 20 relates to an amorphous drug.

The rejection is otherwise traversed, especially on the basis of the amendments Applicants' have made to independent claims 1, 30, 57, 86, 106, and 126. Nakamichi relates to solid dispersions made using a twin screw extruder. Nakamichi goes to great lengths to characterize his twin screw extruded dispersions as being roughly equivalent to dispersions produced by an alternate method, rotary evaporation. No disclosure of formulations which are non-dispersions was made. Applicants claims 1, 30, 57, 86, 106, and 126 have now been amended to reflect that Applicants' formulations are not dispersions, as supported at page 11, lines 19-24. Concerned as Nakamichi is with solid dispersions, one interested in non-dispersion formulations like Applicants' would undoubtedly dismiss Nakamichi out of hand as being irrelevant. Certainly one with knowledge of Nakamichi would miss the advantages of formulations like those of Applicants which comprise non-dispersions. In different language, non-dispersions simply cannot be obvious from a reference which only discloses dispersions.

Claims 146 and 155 have not been amended to exclude dispersions since the claims relate to solutions. It is respectfully submitted that these claims have specific requirements relating to polymer/drug assemblies that are required to have a certain size. Nakamichi simply does not contain disclosure which would fill in the large gaps left by these specific requirements. It is well accepted that for an invention to be obvious over a piece of prior art, the prior art must suggest the differences or, alternatively, suggest the modifications which Applicants have made. Nakamichi suggests nothing about polymer drug assemblies, and certainly mentions nothing about their size. Without a disclosure of these features, Nakamichi cannot support an obviousness rejection. The Examiner is accordingly respectfully requested to reconsider and withdraw the rejection as it relates to these claims.

In view of the above comments, it is respectfully requested that the rejections over Piergiorgio and Nakamichi be withdrawn.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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VERSION MARKED UP TO SHOW CHANGES MADE

The claims have been amended as follows:

1. (Once Amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said solubility-improved form in a sufficient amount so that said composition provides, after introduction to a use environment, a maximum concentration of said drug in said use environment that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug in said use environment that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

said composition not being a dispersion.

30. (Once Amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a dissolution area under the concentration versus time curve in said use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

said composition not being a dispersion.

58. (Once Amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a relative bioavailability of at least 1.25,

said composition not being a dispersion.

86. (Once Amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said solubility-improved form in a sufficient amount, so that after introduction to a use environment, a maximum concentration of said drug in said use environment is provided that is at least 1.25-fold an equilibrium concentration of said drug in said use environment provided by a control composition;

and wherein a concentration of said drug in said use environment is provided that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by said control composition exceeds said equilibrium concentration;

and wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

and provided (a) and (b) are not administered in a dispersion.

106. (Once Amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to a use environment, a dissolution area under the concentration versus time curve is provided in said use environment for a

period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition;

and wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

and provided (a) and (b) are not administered in a dispersion.

126. (Once Amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to a use environment, a relative bioavailability is provided of at least 1.25-fold that of a control composition, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

and provided (a) and (b) are not administered in a dispersion.